

CHAPTER

# 9

## Virology

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## I. INTRODUCTION

### A. General Characteristics of Viruses

1. Viruses are **obligate intracellular parasites unable to self-replicate**. Once inside living cells, viruses induce the host cell to synthesize virus particles.
2. The genome is either **DNA or RNA** (single or double stranded).
3. Viruses do not have a system to produce ATP.
4. Viruses range in size from 25 to 270 nm.
5. The classification of viruses is based on nucleic acid type, size and shape of virion, and presence or absence of an envelope.

### B. Viral Structure

1. **Virion** is the entire viral particle.
2. **Capsid** is the protein coat that encloses the genetic material.
3. **Capsomer** is the protein subunit that makes up the capsid.
4. **Nucleocapsid** is composed of the capsid and genetic material.
5. The **envelope** is the outer coating composed of a **phospholipid bilayer**, which is composed of viral-encoded glycoproteins and sometimes viral-encoded matrix proteins. The envelope is derived from a host cell's membrane. Some viruses use the plasma membrane, whereas others use endoplasmic reticulum, Golgi, or nuclear membranes. **Naked nucleocapsids** are viruses with no envelopes.

### C. Replication

1. **Adsorption** is attachment of the virus to a specific receptor on the host cell.
2. **Pentration** is entry of the virus into the host cell.
3. **Uncoating** occurs when there is either the separation of the capsid from the genome or rearrangement of the capsid proteins exposing the genome for transcription and replication.
4. The **eclipse period** is the stage when the genetic material is replicated but intact virions are not yet detectable.
  - a. Viral DNA or RNA serves as the template for mRNA production.
  - b. mRNA codes for viral protein and enzymes necessary for nucleic acid synthesis.
5. **Assembly (maturation)**: Genetic material is assembled into a protein coat.
6. Viruses are then released from the host cell.
  - a. **Cell lysis**: Naked viruses lyse host cell and leave through a hole in the plasma membrane.
  - b. **Budding**: Intact virion pushes outward from a host's membrane. The membrane wraps around the virion; the membrane is cleaved and then resealed around the virion, thus becoming the viral envelope.

## D. Specimen Processing for Diagnosing Viral Diseases

1. Viruses are in highest concentrations during the first several days following onset of symptoms. Therefore, samples should be collected early in the disease course.
2. Samples should generally come from the infected site.
  - a. **Skin infections:** Rash site and, depending on the virus, serum and urine
  - b. **Respiratory infections:** Sputum or throat swabs
  - c. **Central nervous system** (e.g., meningitis and encephalitis): For diagnosis of meningitis, cerebrospinal fluid (CSF) and serum, as well as stool or throat swabs, can be collected because viruses are sometimes shed into these sites. In cases of encephalitis, brain biopsy material and sometimes serum are used.
  - d. **Urogenital infections:** Needle aspirates and endocervical and urethral swabs
  - e. **Gastrointestinal tract:** Stool samples and rectal swabs
  - f. **Eye infections:** Eye swabs and corneal scrapings

## E. Sample Transport

1. Samples for viral culture must be placed into a **viral transport medium** (VTM).
2. VTM contains:
  - a. Buffered saline
  - b. Protein stabilizers
  - c. Antimicrobials that inhibit bacterial and fungal growth
3. Samples for viral cultures can be refrigerated in VTM for about 48 hours, but they should never be frozen at  $-20^{\circ}\text{C}$ . Samples can be stored at  $-70^{\circ}\text{C}$ ; however, infectivity will be diminished.

# II. SAMPLE SITES AND ASSOCIATED VIRAL AGENTS

## A. Respiratory System

1. **Upper respiratory tract** infections are commonly caused by viruses, including rhinovirus, influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), Epstein-Barr virus (EBV), and coronavirus.
2. **Croup and bronchitis** can be caused by influenza virus, parainfluenza virus, RSV, and adenovirus.
3. **Pneumonia** in children can be caused by **RSV**, parainfluenza virus, adenovirus, and varicella-zoster virus (VZV).
4. **Pneumonia** in adults can be caused by influenza virus, VZV, cytomegalovirus (CMV), and RSV.

## B. Viral Meningitis

1. Caused by enterovirus, echovirus, herpes simplex virus type 1 (HSV-1), HSV-2, and VZV
2. Viral meningitis is often less severe than bacterial meningitis. **Aseptic meningitis** is an older term referring to meningitis not caused by easily cultured bacteria. The term has become synonymous with viral meningitis.

### C. Encephalitis

1. Encephalitis typically has a viral etiology. Infections are caused by HSV, VZV, and **arboviruses**. Arboviruses are genetically unrelated viruses transmitted by arthropods (e.g., mosquitoes); they include the families *Togaviridae* (eastern and western equine viruses) and *Flaviviridae* (St. Louis encephalitis virus). A number of animals, including birds and horses, serve as reservoirs for these viruses. Rabies virus is also an uncommon cause of encephalitis.
2. Encephalitis is an infection of the brain or spinal cord and is much more severe than viral meningitis.

### D. Cutaneous Infections

1. Caused by HSV-1, HSV-2, VZV, echovirus, measles virus, rubella virus, enterovirus, molluscum contagiosum virus, and parvovirus B-19
2. Cutaneous infections often result in a rash that, depending on the virus, can have a variety of presentations.

### E. Genital Infections (Urethritis, Cervicitis, etc.)

1. Frequently caused by HSV-2 and human papillomavirus
2. Genital tract infections are typically sexually transmitted.

### F. Gastroenteritis

1. Caused by a number of viruses, including **rotaviruses**, **Norwalk viruses**, adenoviruses, and calciviruses
2. The symptoms can range from mild self-limiting diarrhea to severe diarrhea with dehydration, particularly with **rotavirus** infections in young children.

### G. Eye Infections

1. Caused by HSV, adenovirus, and VZV
2. Viruses can cause conjunctivitis and severe cases of keratitis, resulting in blindness.

### H. Neonatal Infections

1. Neonatal infections are acquired *in utero*, during childbirth, or soon after childbirth.
2. The infections can be caused by HSV, CMV, and rubella virus.

## III. VIRAL IDENTIFICATION

### A. Histology and Cytology

1. Cellular inclusions are diagnostic for many viruses.
2. Because most **DNA viruses** replicate in the nucleus, they often produce nuclear inclusions. However, some DNA viruses are assembled elsewhere in the cell.
3. **RNA viruses** produce cytoplasmic inclusions (assembled in the cytoplasm).

4. HSV and VZV cause intranuclear inclusions. CMV induces enlarged (cytomegalic) cells with a basophilic intranuclear inclusion referred to as “**owl eye**” inclusion.

## B. Viral Isolation

### 1. Cell culture

- a. Cell culture is an important means of diagnosing viral infections. Cell cultures require nutritionally rich complex media. The media often contain fetal calf serum as a nutrient. Clinical specimens are processed and added to the cell cultures. Viruses have an affinity for specific cell types (e.g., respiratory epithelium, neurons, etc.). Propagation of viruses is therefore dependent upon providing suitable host cells. Some viruses have not yet been grown *in vitro*.
  - b. **Primary cell cultures** are derived directly from tissue. These cells have a normal number of chromosomes (diploid) and are permissive for a number of viruses, but they can only be maintained for a short time in the laboratory. An example of a primary cell line is primary monkey kidney cells. Transferring cells from one container (e.g., test tube or flask) to another is called “**splitting**” or “**passaging**.” Primary cell lines can only be passaged a few times. They are used to grow influenza virus, parainfluenza virus, enteroviruses, and adenoviruses.
  - c. **Established cell lines**, also referred to as low passage or finite cell lines, are also diploid. They can be maintained longer than primary cell lines, but they are not as permissive. Examples of established cell lines include WI-38, MRC-5, and IMR-90.
  - d. **Continuous cell lines** are altered cells that can be maintained indefinitely. These cells are **heteroploid**, having an abnormal karyotype from the original parent tissue. HeLa, HEP-2, A549, and Vero cells are examples of continuous cell lines. They can be used to grow HSV, VZV, CMV, adenovirus, and rhinoviruses.
  - e. Slides are made from infected cell cultures and examined for cellular changes, including clumping, vacuoles, inclusions, granules, cell fusion (i.e., **syncytium**—multinucleated cell development), and cellular destruction. These visible changes are referred to as **cytopathic effect** (CPE). However, many viruses replicate without producing CPE.
2. Embryonated eggs are sometimes used for growth of viruses. Eggs are not typically used for diagnosis of viral infection but to cultivate viruses for research studies and vaccine preparation, as in the case of influenza virus.
  3. Animal models are sometimes used in research studies.

## C. Electron Microscopy

1. Due to size, most individual virions can only be seen by electron microscopy. However, the poxviruses are about the size of some small bacteria.

2. Electron microscopy is sometimes used to identify Norwalk viruses, astrovirus, calicivirus, and coronavirus. Electron microscopy is expensive, requires expertise, and is usually not very sensitive. For these reasons, electron microscopy is not commonly used.

**D. Other Methods for Identification**

1. Detection of host antibodies directed against specific viruses
2. Direct detection of viral antigens in clinical specimens
3. Viral gene probes and nucleic acid amplification (e.g., polymerase chain reaction [PCR])

**IV. MEDICALLY IMPORTANT DNA VIRUSES**

**A. Herpesviruses**

1. **General characteristics**
  - a. Herpesviruses are icosahedral shaped, have an envelope, and range in size from 90 to 100 nm. Table 9-1 ■ lists some medically important DNA viruses.
  - b. They are members of the family *Herpesviridae*.
  - c. Except for neonates, infections are more severe in adults than in children.
  - d. All herpesviruses produce **latent infections**.
  - e. Sites of latency include **leukocytes** and **peripheral nerves**.
  - f. **Reactivation** may result from physiological stress. The symptoms are milder than primary infection. The exception is shingles, which is a reactivation of VZV.

TABLE 9-1 FAMILIES OF DNA VIRUSES	
Family	Important Human Viruses
<i>Poxviridae</i>	Variola virus, molluscum contagiosum virus
<i>Herpesviridae</i>	Herpes simplex viruses types 1 and 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human herpesviruses 6, 7, and 8
<i>Adenoviridae</i>	Adenovirus
<i>Hepadnaviridae</i>	Hepatitis B virus
<i>Papillomaviridae</i>	Papillomavirus
<i>Polyomaviridae</i>	JC and BK viruses
<i>Parvoviridae</i>	Parvovirus B19

TABLE 9-2 MAJOR CLINICAL SYNDROMES OF HUMAN HERPESVIRUSES

Virus	Major Clinical Syndrome	Site of Latent Infection
Herpes simplex virus Type 1	Gingivostomatitis in children and young adults, recurrent oral-labial infection (cold sores), infection of the cornea (keratitis), herpes encephalitis	Trigeminal nerve root ganglion and autonomic ganglia of superior cervical and vagus nerves
Type 2	Genital herpes, neonatal herpes	Sacral nerve root ganglia
Varicella-zoster	Chickenpox (primary infection), shingles or zoster (reactivation)	Thoracic, cervical or lumbar nerve root ganglia
Cytomegalovirus	Asymptomatic infection, heterophile-negative mononucleosis, fever hepatitis syndrome in neonates and transplant patients, interstitial pneumonia in immunocompromised patients	Leukocytes (neutrophils and lymphocytes)
Epstein-Barr virus	Heterophile-positive mononucleosis	B lymphocytes
Human herpesvirus 6	Roseola (sixth disease)	Peripheral blood mononuclear cells
Human herpesvirus 7	Roseola and febrile disease in children	Peripheral blood mononuclear cells
Human herpesvirus 8	Kaposi's sarcoma	Peripheral blood mononuclear cells

g. Herpesviruses include VZV, HSV-1 and -2, CMV, EBV and human herpes viruses 6, 7, and 8 (HHV-6, -7, and -8). Table 9-2 ■ lists important clinical manifestations associated with the herpesviruses.

## 2. Herpes simplex virus type 1

- HSV-1 causes mouth lesions and **fever blisters** (i.e., cold sores). Most cases are very mild, and symptoms may include mild fever and general malaise. Infections can also be asymptomatic.
- Diagnosis** is by clinical symptoms, immunologic assays that detect viral antigens, and viral isolation.
- HSV will grow in continuous cell lines (e.g., HEp-2 and A549) and established cell lines (e.g., MRC-5). In A549 cells, **syncytia** are sometimes seen; although they are more frequently found with HSV-2. MRC-5 infected cells develop cytoplasmic granules that become large, round, and refractile (**balloon cells**). Clusters (foci) of infected cells appear in a few days.



### 3. **Herpes simplex virus type 2**

- a. HSV-2 is a causative agent of genital herpes, a common sexually transmitted disease (STD). HSV-1 causes about 20% of genital herpes cases.
- b. Lesions appear on the penis, cervix, and vagina.
- c. HSV has been linked to cervical carcinoma; however, human papillomaviruses are a much more common cause.
- d. Infant infection acquired during childbirth can cause severe eye infections and central nervous system (CNS) damage.
- e. **Diagnosis** is by clinical symptoms, immunologic assays that detect viral antigens, viral isolation, and sometimes serology.

### 4. **Varicella-zoster virus**

#### a. **Chickenpox**

- 1) Chickenpox is primarily a childhood illness; however, symptoms are more severe in adults.
- 2) Infection is spread by respiratory aerosol from vesicular skin lesions of infected individuals.
- 3) The incubation period is from 1 to 2 weeks.
- 4) Symptoms include a rash and fever.
- 5) Individuals are contagious 48 hours before the rash and will remain contagious until scabbing of all lesions.
- 6) The routine use of a vaccine has greatly reduced the incidence of chickenpox.

#### b. **Shingles**

- 1) **Reactivation** of VZV in the peripheral or cranial nerves leads to shingles and occurs mainly in the elderly.
- 2) Characterized by skin vesicles, often on one side of the body, and severe pain around the skin lesions
- 3) Complications include CNS disorders, eye problems, and facial paralysis.
- 4) **Diagnosis** is often based on clinical symptoms.

### 5. **Cytomegalovirus**

- a. CMV causes infections that are typically **asymptomatic**. Severe infections can occur in immunocompromised patients and can include pneumonia and encephalitis.
- b. Congenital infections are severe and cause developmental problems for the newborn.
- c. The virus is transmitted through contact with saliva or blood.
- d. CMV results in persistent infections in humans, including endothelial cells and leukocytes. The tubular cells of the human kidney shed CMV for prolonged periods into the urine.
- e. **Diagnosis** is by serologic testing or viral isolation from blood, respiratory secretions, or urine. The virus grows best in human fibroblast cells (e.g., WI-38 and MRC-5), where it will produce characteristic intranuclear inclusions previously described.



## 6. Epstein-Barr virus

- a. EBV causes **infectious mononucleosis**, a common but relatively mild disease. It is also associated with **Burkitt lymphoma**, **nasopharyngeal carcinoma**, and Hodgkin disease and other lymphomas.
- b. The virus is transmitted in **saliva**. The incubation period lasts 1–2 months.
- c. **Symptoms** include fever, enlarged lymph nodes, and swollen tonsils.
- d. **Diagnosis**
  - 1) Signs and symptoms
  - 2) Hematologic abnormalities include lymphocytosis and the presence of reactive (atypical) lymphocytes.
  - 3) Serology
    - a) **Heterophile antibodies:** Individuals with EBV infection produce antibodies that will agglutinate sheep and horse red blood cells. These assays are effective in diagnosing about 85% of infectious mononucleosis cases.
    - b) Viral-specific antibody assays may be necessary in the roughly 15% of the patients with infectious mononucleosis that do not produce heterophile antibodies.

## 7. Human herpesvirus 6

- a. HHV-6 is a very common virus and is acquired by respiratory secretions.
- b. HHV-6 infects T lymphocytes.
- c. Infections are generally mild or subclinical in immunocompetent individuals. HHV-6 causes exanthem subitum, also known as **roseola** or **sixth disease**.
- d. Sixth disease is a childhood disease characterized by fever, rash, and sore throat; neurologic involvement is rare.

## 8. Human herpesvirus 7

- a. HHV-7 is also a very common virus, with serologic prevalence rates in healthy adults about 90%.
- b. The virus is mostly transmitted via saliva and infects lymphocytes.
- c. In immunocompetent individuals, infections are mild or asymptomatic. HHV-7 causes about 5% of all cases of roseola; neurologic involvement is rare.

## 9. Human herpesvirus 8

- a. HHV-8 is associated with Kaposi sarcoma in immunosuppressed patients (e.g., acquired immunodeficiency syndrome [AIDS]) and is also known as Kaposi sarcoma herpes virus (KSHV).
- b. The virus is probably transmitted via oral secretions.
- c. Little is known about primary HHV-8 infections. In latent infections, viral DNA has been found in B cells and peripheral blood mononuclear cells.

## B. Human Papillomavirus (HPV)

1. HPV has an icosahedral shaped, enveloped virion. The viruses range in size from 40 to 55 nm.

2. Member of the family *Papillomaviridae*
3. HPV causes plantar warts, genital warts, and flat warts. Some HPVs are **associated with cervical cancer**. Genital warts are the most common STD in the U.S., and HPV is the most common cause of cervical cancer.
4. A **vaccine** was recently approved for use in females. The vaccine, designed to prevent cervical cancer, contains the strains of HPV most often associated with this disease.

### C. Poxviruses

1. Identifying characteristics
  - a. Poxviruses are large, ranging in size from 220 to 450 nm.
  - b. Virions also contain a DNA polymerase for DNA replication and an RNA polymerase system for transcription of viral genes. Poxviruses replicate entirely within the cytoplasm.
  - c. Poxviruses belong to the family *Poxviridae*.
2. **Variola virus**
  - a. **Variola major** caused a severe disease known as smallpox that had a fatality rate of about 30%. **Variola minor** strains produced milder infections with a fatality rate of less than 1%.
  - b. Due to a worldwide vaccination program, the World Health Organization was able to declare the world smallpox free in 1979. The **vaccinia virus** is an attenuated vaccine that prevents variola infection.
  - c. Variola virus is considered a potential **bioterrorism agent**.
3. Other poxviruses
  - a. **Molluscipoxvirus** causes **molluscum contagiosum**, a skin infection that occurs worldwide.
  - b. **Monkeypox virus** causes a **zoonosis** found primarily in Africa. An outbreak recently occurred in the U.S. Infections were traced back to rodents imported from Africa that transmitted the virus to prairie dogs.

### D. Adenoviruses

1. Identifying characteristics
  - a. Adenoviruses are naked icosahedral virions. They range in size from 70 to 90 nm.
  - b. Adenoviruses belong to the family *Adenoviridae* and have been isolated from humans and animals.
2. **Infections**
  - a. **Respiratory tract infections**, especially in young children
  - b. **Urinary tract and gastrointestinal infections**, and pharyngitis
  - c. **Eye infections** in newborns, immunocompromised patients, and military recruits (because of close living conditions) are common. Adenoviruses have been associated with epidemics of keratoconjunctivitis.
3. **Sample collection:** Throat swabs, eye samples, and stool

## V. MEDICALLY IMPORTANT RNA VIRUSES

### A. Retroviruses

1. The retroviruses have an icosahedral shaped, enveloped virion. They range in size from 80 to 130 nm. Some medically important RNA viruses are listed in Table 9-3 ■.
2. Retroviruses contain an RNA-dependent DNA polymerase (**reverse transcriptase**) for replication. Reverse transcriptase uses viral RNA as a template to make double-stranded DNA that then moves into the nucleus where it is integrated into the host chromosome. This stage is referred to as a **provirus**. The genome is transcribed into mRNA by host RNA polymerase.

TABLE 9-3 FAMILIES OF RNA VIRUSES

Family	Important Human Viruses
<i>Paramyxoviridae</i>	Measles, mumps, respiratory syncytial, parainfluenza, and metapneumo viruses
<i>Orthomyxoviridae</i>	Influenza A, B, and C viruses
<i>Coronaviridae</i>	Coronavirus
<i>Arenaviridae</i>	Lymphocytic choriomeningitis and Lassa fever viruses
<i>Rhabdoviridae</i>	Rabies virus
<i>Filoviridae</i>	Marburg and Ebola viruses
<i>Bunyaviridae</i>	California encephalitis, Hantaan, sin nombre, and Crimean-Congo viruses
<i>Retroviridae</i>	Human T lymphotropic and human immunodeficiency viruses
<i>Reoviridae</i>	Rotavirus and reovirus
<i>Picornaviridae</i>	Rhinovirus, poliovirus, enterovirus, ECHO virus, coxsackievirus, hepatitis A virus
<i>Togaviridae</i>	Rubella virus and western, eastern, and Venezuelan equine encephalitis viruses
<i>Flaviviridae</i>	Yellow fever, dengue, St. Louis encephalitis, hepatitis C, and West Nile viruses
<i>Caliciviridae</i>	Norwalk and Sapporo viruses

### 3. Lentiviruses

- a. The **human immunodeficiency virus 1** (HIV-1) and HIV-2 are members of the genus *Lentivirus*.
- b. **HIV** is the causative agent of **AIDS**. HIV-1 causes a more severe infection and is much more prevalent than HIV-2.
- c. **Spread of the virus** is by sexual contact with infected individuals (homosexual or heterosexual), intravenous drug use, congenital transmission, or contaminated blood products.
- d. The virus initially infects macrophages and dendritic cells, then the host's **CD4 positive T cells**. These cells are key to both humoral-mediated and cell-mediated immune responses. As more T cells are destroyed, immune function deteriorates. CD4 is the primary receptor for the virus; important coreceptors include CXCR4 and CCR5.
- e. **Acute infections** are often mild and can resemble infectious mononucleosis. Acute infections are rarely diagnosed. Virus replication occurs at a high rate in lymphoid tissue, but the patient remains asymptomatic for many years. The host is able to replace infected T cells as fast as they are destroyed. This condition is referred to as **“clinical latency.”**
- f. Eventually, the virus begins to destroy T cells faster than they can be replaced. As immune function is compromised, the patient presents with chronic and recurrent infections, including *Pneumocystis* pneumonia, CMV infections, mycobacteriosis, cryptosporidiosis, candidiasis, and toxoplasmosis. This stage is sometimes referred to as **AIDS-related complex**.
- g. As immune function continues to deteriorate, the infections become more severe and life threatening. This stage is referred to as **AIDS** or **full-blown AIDS**.
- h. HIV has also been associated with malignant conditions such as **Kaposi sarcoma**, cancer, and B cell lymphomas.
- i. **Diagnosis** is by clinical history, serology, and detection of viral antigens or RNA.
- j. Most serologic tests are **screened using an ELISA**; all reactive samples are repeated in duplicate. **Repeatedly reactive samples** must be confirmed, generally by the **Western blot assay**. Once a patient is determined to be positive for HIV, the stage of the disease is then determined. **Staging** is based on CD4-positive cell counts and the presence of various opportunistic infections. Viral load can be determined by reverse transcriptase-polymerase chain reaction (RT-PCR).

### 4. Human T-cell lymphotropic virus (HTLV)

- a. This group of viruses includes HTLV-1 and HTLV-2.
- b. These viruses are transmitted via sexual contact, mother to child by breast feeding, and parenteral drug use.

- c. HTLV-1 has been linked to **adult T cell leukemia** and **HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)**.
- d. Although HTLV-2 has not been associated with malignancies, it has been linked to a neurologic disease resembling HAM/TSP.

## B. Orthomyxoviruses

1. Orthomyxovirus virions contain a segmented RNA genome and have a helical-shaped virion with an envelope. They range in size from 75 to 125 nm.
2. The **influenza viruses**, A, B, and C, are the only members of the family *Orthomyxoviridae*.
3. Orthomyxoviruses have **hemagglutinin (HA)** and **neuraminidase (NA)** on their surface. These molecules are immunogenic, and antibodies to these molecules confer protection. HA allow the viruses to attach to the surface of respiratory epithelial cells and also agglutinate red blood cells. NA has enzymatic activity, cleaving budding viruses from infected cells.
4. **Antigenic drift** occurs when point mutations occur in the viral genes encoding the HA and NA spikes. Antigenic drift can occur within any of the three influenza viruses.
5. **Antigenic shift** occurs following a major change (reassortment) of the RNA genome when a single host cell is infected with two different influenza viruses. Among the influenza viruses, antigenic shift only occurs in influenza A viruses. Antigenic shift results in a new combination of viral surface glycoproteins (e.g., from H1N1 to H2N1). Influenza A can infect other animals, including birds and pigs. In these animals, the virus often undergoes recombination events, resulting in new strains. Epidemics and pandemics are generally due to antigenic shifts. Other viruses, such as HIV, can also undergo antigenic shift.
6. An **influenza trivalent vaccine** is available; each year the formulation of the vaccine can vary as the Centers for Disease Control and Prevention tries to predict which influenza strains will predominate in the upcoming flu season.
7. **Diagnosis** is based on clinical symptoms, serology, direct antigen detection, and viral isolation.

## C. Paramyxoviruses

1. Paramyxoviruses have helical-shaped enveloped virions. They range in size from 150 to 300 nm.
2. The family *Paramyxoviridae* contains paramyxoviruses, morbilliviruses, pneumoviruses, and megamyxoviruses.
3. **Parainfluenza viruses** cause childhood **croup**, which is a respiratory infection characterized by fever and a hoarse cough. There are four human parainfluenza viruses: 1–4.

4. **Mumps**, caused by the **mumps virus**, is an infection of the **parotid glands**, causing swelling and difficulty in swallowing. Mumps is rare in developed countries because of widespread use of a vaccine.
5. **Morbillivirus** causes **rubeola** or **measles**, typically a childhood illness. Necrotic vesicles with a white center surrounded by erythema on the oral mucosa, referred to as **Koplik spots**, are a characteristic of measles. Vaccination programs have nearly eliminated measles in developed countries.
6. **Respiratory syncytial virus** (RSV) is a member of the genus *Pneumovirus*.
  - a. RSV causes respiratory and ear infections that are most common in newborns and young children. Worldwide, it is the most common cause of bronchitis and pneumonia in infants and children.
  - b. RSV is characterized by the formation of **syncytia**. An infected cell can cause fusion with adjacent cells, producing giant multinucleated cells. The virus can be grown in human heteroploid cells such as HEp-2, HeLa, and A549.

#### D. Picornaviruses

1. The picornaviruses have a naked virion ranging in size from 20 to 30 nm.
2. The family *Picornaviridae* includes a number of viruses such as the enteroviruses, hepatitis A virus, and the rhinoviruses.
3. **Enteroviruses**
  - a. Members of the genus *Enterovirus* (e.g., poliovirus, coxsackie viruses, and echoviruses) are a common cause of a variety of human infections worldwide. They most commonly produce an acute nonspecific febrile syndrome. Enteroviruses also cause infections of the respiratory and gastrointestinal tracts.
  - b. **Diagnosis** is generally made by nucleic acid amplification tests of clinical specimens: serum, CSF, throat swabs, rectal swabs, etc.
4. **Poliovirus**
  - a. Poliovirus is transmitted by the **fecal-oral route**. The virus initially infects the gastrointestinal tract but spreads to the CNS. Most infections are mild but can result in meningitis or **paralytic polio**.
  - b. **Vaccines**
    - 1) The **Salk vaccine** is a formalin-inactivated vaccine.
    - 2) The **Sabin vaccine** is an attenuated vaccine.
    - 3) Because of vaccination programs, the current risk for polio is extremely small. The Sabin vaccine produces a stronger immune response. However, because the attenuated virus can sometimes produce severe infection, most countries now routinely use the Salk vaccine.
5. **Coxsackie virus**
  - a. Coxsackie A viruses cause **hand, foot, and mouth disease of humans**; this is not the same disease as foot and mouth disease of animals. Coxsackie A virus is also associated with conjunctivitis.
  - b. Coxsackie B viruses cause about one-third of all cases of **myocarditis**. They are also associated with meningitis.

## 6. Rhinoviruses

- a. Rhinoviruses are a frequent cause of the **common cold**. Other viruses, including coronaviruses, are also associated with colds. The rhinoviruses grow better at temperatures just below core body temperature (e.g., 33°C). This is near the typical temperature of the nasal passage.
- b. Over 100 serotypes are known, and immunity to one does not provide immunity to the others. This is why colds are so common.
- c. Infection prevention includes handwashing and avoiding hand-to-nose contact.

## E. Rotaviruses

1. Rotaviruses have a double-stranded RNA genome. The virion is about 70 nm in diameter and has a **wheel-like (spokes) appearance**. Rotaviruses belong to the family *Reoviridae*.
2. Rotaviruses are the most important cause of gastrointestinal infections in children less than 2 years of age.
3. **Diagnosis:** Antigen detection via latex agglutination or ELISA and, less commonly, immunoelectron microscopy

## F. Caliciviridae

1. The family *Caliciviridae* contains four genera: *Norovirus*, *Sapovirus*, *Lagovirus*, and *Vesivirus*. They are small, naked viruses.
2. The noroviruses and Norwalk viruses (members of the genus *Norovirus*) are highly contagious and are important causes of gastroenteritis.

## G. Togaviridae

1. The virions are about 70 nm in diameter and contain an envelope.
2. The family *Togaviridae* contains two genera.
  - a. *Rubivirus*: **Rubella virus** is the only member of this genus. The virus causes a mild infection. However, it can produce severe **congenital infections** if women are infected in the early stage of pregnancy, therefore, pregnant women and women of childbearing age are often tested for immunity. Rubella is rare in developed countries because of an effective vaccine.
  - b. *Alphavirus*: This genus contains about 25 viruses, all of which are transmitted by arthropods.

## H. Flaviviridae

1. Many viruses belonging to the family *Flaviviridae* are arboviruses. Important members of this family include West Nile virus (WNV), St. Louis encephalitis virus, yellow fever virus, and dengue virus.
2. **West Nile virus**
  - a. First reported in the U.S. in 1999 in New York
  - b. Birds are the primary reservoir for WNV, and mosquitoes are the vectors.



- c. WNV typically produces mild or asymptomatic infections in many otherwise healthy individuals. However, the most serious complication of WNV infection is fatal encephalitis (inflammation of the brain). In 2007, 124 people died of WNV infection in the U.S.
- d. Laboratory diagnosis of WNV infection can be made by ELISA antigen capture RT-PCR.

### I. Rhabdovirus

- 1. Rhabdoviruses have a bullet-shaped, enveloped capsid ranging in size from 150 to 350 nm.
- 2. Rabies virus, a member of the family *Rhabdoviridae* and the genus *Lyssavirus*, causes **rabies**.
- 3. The rabies virus gains entry into humans by animal (e.g., cat, dog, or raccoon) bites, as well as contact with bats. The virus first infects the muscle tissue but preferentially infects neurons. The virus migrates along the peripheral nerves to the **CNS**. The disease progresses to produce convulsions, coma, and fatal encephalitis.
- 4. **Diagnosis** is through medical history of animal bites and a positive direct fluorescent-antibody test. Detection of **Negri bodies** in infected brain cells has a low sensitivity and is not recommended. Negri bodies are virus inclusions inside infected cells.
- 5. A rabies **vaccine** is available to prevent infection. It is only administered to those at risk for exposure to the rabies virus.
- 6. Post-exposure treatment is effective if administered within 72 hours. Without rapid treatment, the infection is essentially 100% fatal.

### J. Filoviridae

- 1. Virions range in size from 800 to 1000 nm.
- 2. The family *Filoviridae* includes the **Marburg** and **Ebola** viruses.
- 3. Bats are thought to be the reservoir, but the mode of transmission is unclear.
- 4. Infection by these viruses produces **hemorrhagic fever** with high fatality rates.
- 5. Most cases occur in Africa.

## VI. HEPATITIS VIRUSES

### A. Hepatitis A Virus (HAV)

- 1. **Identifying characteristics**
  - a. HAV contains RNA, and the naked virion has an icosahedral shape. HAV ranges in size from 24 to 30 nm.
  - b. It is a member of the family *Picornaviridae* and the genus *Hepatovirus*. Table 9-4 ■ summarizes other important causes of hepatitis.

TABLE 9-4 IMPORTANT HUMAN HEPATITIS VIRUSES

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Family	<i>Picornaviridae</i>	<i>Hepadnaviridae</i>	<i>Flaviviridae</i>	Unclassified	<i>Hepeviridae</i>
Genome	RNA	DNA	RNA	RNA	RNA
Transmission	Fecal-oral	Parenteral, blood, sexually, needles, perinatal	Parenteral, blood, needles, perinatal	Parenteral, blood, sexually, needles, perinatal	Fecal-oral
Comments	No chronic liver disease, rarely fatal, severity increases with age	5–10% chronic hepatitis, associated with hepatocellular cancer	Chronic infections are common	Coinfection/ superinfection in patients infected with HBV	Wide range of clinical outcomes, high mortality rate in pregnant women

## 2. Infections

- Infections are spread by the **fecal-oral route** and are generally due to poor sanitation and hygiene. Food handling transmission is common.
- Humans can also acquire the infection from contaminated shellfish, including shrimp, oysters, scallops, etc.
- Vaccines are available.**

## 3. Clinical characteristics

- The incubation period is 15–40 days.
- Liver involvement (jaundice), nausea, anorexia, and malaise
- Mortality rate is less than 1%.

## 4. Diagnosis

- Clinical symptoms and liver enzymes, particularly alanine aminotransferase, are elevated.
- Serology

## 5. Serologic indicators

- Anti-HAV IgM is positive in acute infections.
- Anti-HAV IgG (positive) and anti-HAV IgM (negative) indicate a past HAV infection.
- General serology testing also includes ruling out hepatitis B virus.

## B. Hepatitis B Virus (HBV)

### 1. Identifying characteristics

- HBV contains partially double-stranded DNA. The complete virion has an envelope, ranges in size between 42 and 47 nm, and is sometimes referred to as **Dane particles**.

- b. The virus is unusual in that an RNA intermediate is required for replication of the genome. The virus needs a viral-encoded reverse transcriptase for replication.
  - c. Member of the family *Hepadnaviridae*
- 2. **Infections**
  - a. Infections are spread by contaminated body fluids, including blood. HBV can be sexually transmitted.
  - b. Infections are associated with contaminated blood products, needle sticks, tattoos, body piercing, intravenous drug abuse, and renal dialysis.
  - c. HBV vaccines are available and are recommended for all healthcare workers.
- 3. **Clinical characteristics**
  - a. The incubation period is 50–180 days.
  - b. **Acute infections** produce symptoms resembling HAV infections.
  - c. **Chronic infections** are common and can result in **cirrhosis** and **hepatocellular carcinoma**.
- 4. **Diagnosis**
  - a. Clinical symptoms and elevated liver enzymes
  - b. Serology
- 5. **Serologic indicators**
  - a. **Hepatitis B surface antigen** (HBsAg) is the first marker to be positive, but it will become negative as the patient recovers. In **chronic infections**, HBsAg will remain positive. Presence of this marker indicates that the patient is infectious.
  - b. **Antibody to HBsAg** (anti-HBs) indicates **recovery or immunity** after HBV vaccination. The antibody is generally present for life.
  - c. **IgM antibody to HB core antigen** (anti-HBc IgM) indicates recent **acute infection**. As anti-HBs is forming, the level of HBsAg is decreasing. During this transition, there is a point when both markers are undetectable. At this time, the only indicator of HBV infection is anti-HBc IgM; this is called the “**core window**.”
  - d. Total antibody to HBcAg is positive in acute infection stages. It also indicates current or past infections but does not indicate recovery or immunity.
  - e. **HBeAg** is positive in acute and chronic stages of infection. Presence of this marker also indicates that the patient is infectious.
  - f. **Anti-HBe** is associated with a good prognosis.

### C. Hepatitis D Virus (HDV)

- 1. HDV contains RNA, and the naked viruses range in size from 35 to 37 nm.
- 2. HDV is also called the **delta virus**. HDV requires but does not encode for HBsAg; therefore, it only replicates in cells also infected with HBV.

3. **Coinfection** occurs when an individual acquires both HDV and HBV at the same time. A **superinfection** is when a patient with an HBV infection is exposed to HDV. Superinfections are more severe than coinfections.
4. **Diagnosis**
  - a. Detection of anti-HDV and HDV RNA
  - b. Serologic markers for HBV will also be positive; in particular, HBsAg.

#### D. Hepatitis C Virus (HCV)

1. **Identifying characteristics**
  - a. HCV contains RNA and has a lipid envelope.
  - b. The virus is a member of the family *Flaviviridae* and the genus *Hepacivirus*.
2. **Infections**
  - a. HCV is the most common cause of **non-A, non-B (NANB) hepatitis**. It is common worldwide.
  - b. Spread through contaminated blood products, organ transplants, renal dialysis, and intravenous drug abuse
  - c. No vaccine currently exists for HCV.
3. **Clinical characteristics**
  - a. The incubation period is 2–25 weeks.
  - b. **Acute** HCV infection is often mild or asymptomatic and is rarely diagnosed in this phase. HCV is more likely to cause **chronic hepatitis**, resulting in cirrhosis, than HBV. HCV infection is one of the most common reasons for liver transplant in the U.S.
4. **Diagnosis**
  - a. Elevated liver enzymes
  - b. **Serologic indicators** (anti-HCV and HCV antigen) and **nucleic acid amplification**
  - c. The virus has not been grown in cell cultures.

#### E. Other Human Hepatitis Viruses

1. **Hepatitis E virus (HEV)**
  - a. HEV contains RNA, and virions range in size from 32 to 34 nm.
  - b. HEV is spread by the **fecal-oral route**, often in contaminated water. It is the most common cause of hepatitis in some countries with poor sanitation.
  - c. Diagnosis: Serology
2. **Hepatitis G virus (HGV)**
  - a. HGV contains RNA and has an envelope.
  - b. It is in the same family, *Flaviviridae*, as HCV.
  - c. Although HGV is most commonly transmitted by contact with blood, it can also be sexually transmitted and transmitted from mother to children. Infection seems to be relatively common worldwide, but HGV is believed to be nonpathogenic.



review

## questions

**INSTRUCTIONS**

Each of the questions or incomplete statements that follows is comprised of four suggested responses. Select the *best* answer or completion statement in each case.

1. The retrovirus responsible for causing acquired immune deficiency syndrome is a member of the family
  - A. *Orthomyxoviridae*
  - B. *Paramyxoviridae*
  - C. *Retroviridae*
  - D. *Flaviviridae*
2. The appearance of Koplik spots in the oral mucosa of patients is characteristic of infection with what viral agent?
  - A. Hepatitis
  - B. Measles
  - C. Rabies
  - D. Smallpox
3. Characteristics of this DNA hepatitis virus include infections spread by contaminated body fluids, 50- to 180-day incubation period, and chronic infections.
  - A. HAV
  - B. HBV
  - C. HCV
  - D. HEV
4. Which of the following has been declared eradicated by the World Health Organization?
  - A. Smallpox
  - B. Human T cell lymphotropic virus
  - C. Hepatitis G virus
  - D. Eastern equine encephalitis
5. Rotavirus is the most common etiologic agent of
  - A. Acute nonbacterial encephalitis in children
  - B. Acute nonbacterial gastroenteritis in infants and young children
  - C. Chronic nonbacterial pharyngitis in children and young adults
  - D. Chronic nonbacterial retinitis in children
6. Kaposi sarcoma is associated with infection by
  - A. Adenovirus
  - B. Cytomegalovirus
  - C. Hepatitis E virus
  - D. Human herpes virus 8

7. The molecular receptor of the virus causing acquired immune deficiency syndrome is
  - A. CD 4
  - B. CD 8
  - C. Fc receptor
  - D. Complement receptor
8. The type of cell culture that best supports the growth of cytomegalovirus is
  - A. HeLa cells
  - B. HEp-2 cells
  - C. Human fibroblast cells
  - D. Primary monkey kidney (PMK) cells
9. Which of the following viruses is predominantly associated with respiratory disease and epidemics of keratoconjunctivitis?
  - A. Adenovirus
  - B. Molluscum contagiosum virus
  - C. Norwalk virus
  - D. Rotavirus
10. A 25-year-old patient presented with multiple vesicles around the mouth. Material from the lesions was obtained by needle aspiration and inoculated to MRC-5 cells. After 1 day, the cytopathic effect included foci of “ballooned” and lysed cells. These observations suggest infection with
  - A. Adenovirus
  - B. Cytomegalovirus
  - C. Epstein-Barr virus
  - D. Herpes simplex virus
11. The Sabin polio vaccine uses which of the following?
  - A. Formalin-inactivated viruses
  - B. Attenuated viruses
  - C. Recombinant viral antigens
  - D. DNA
12. Which of the following is caused by a herpes virus?
  - A. Cold sores
  - B. Hemorrhagic fever
  - C. Polio
  - D. Rabies
13. Which of the following is *not* a general characteristic of a virus?
  - A. Obligate intracellular parasite
  - B. Does not produce ATP
  - C. Genome is surrounded by a protein coat
  - D. Can self-replicate in the appropriate host cell
14. The viral disease shingles, which causes extreme tenderness along the dorsal nerve roots and a vesicular eruption, has the same etiologic agent as
  - A. Rubeola
  - B. Vaccinia
  - C. Varicella
  - D. Variola
15. The etiologic agents of many common colds are RNA viruses that grow better at 33°C than at 37°C. These viruses are
  - A. Adenoviruses
  - B. Orthomyxoviruses
  - C. Paramyxoviruses
  - D. Rhinoviruses
16. Influenza A virus undergoes recombination events that produce new strains; this is referred to as
  - A. Antigenic drift
  - B. Antigenic shift
  - C. Reactivation
  - D. Viral latency
17. Negri bodies may be found in brain tissue of humans or animals infected with
  - A. Adenovirus
  - B. Filovirus
  - C. Measles virus
  - D. Rabies virus

18. Molluscum contagiosum virus is a member of the
  - A. Adenoviruses
  - B. Herpesviruses
  - C. Papovaviruses
  - D. Poxviruses
19. A clinical specimen is received in viral transport medium for viral isolation. The specimen cannot be processed for 72 hours. At what temperature should it be stored?
  - A.  $-80^{\circ}\text{C}$
  - B.  $-20^{\circ}\text{C}$
  - C.  $4^{\circ}\text{C}$
  - D.  $22^{\circ}\text{C}$
20. Arboviruses
  - A. Only infect humans
  - B. Often cause hepatitis
  - C. Typically infect lymphocytes
  - D. Are transmitted by arthropods
21. Mumps is characterized by an infection of the
  - A. Central nervous system
  - B. Parotid glands
  - C. Pancreas
  - D. Thymus
22. Which of the following hepatitis viruses is typically transmitted by the fecal-oral pathway?
  - A. HAV
  - B. HBV
  - C. HCV
  - D. HGV
23. Enteroviruses are most often associated with
  - A. Acute nonspecific febrile syndrome
  - B. Bronchitis and pneumonia
  - C. Lower respiratory tract infections
  - D. Upper respiratory tract infections
24. The “core window” refers to the time
  - A. During hepatitis B virus infection when anti-HBc IgM is the only serologic marker
  - B. During hepatitis B virus infection when HBc is the only serologic marker
  - C. During hepatitis A virus infection when HAc is the only serologic marker
  - D. During hepatitis C virus infection when the virus is latent
25. Human herpesviruses 6 and 7 are associated with a childhood disease called
  - A. Chickenpox
  - B. Measles
  - C. Roseola
  - D. Zoster
26. A baby was admitted to the hospital in February for dehydration due to severe diarrhea. Cultures for bacterial pathogens revealed normal fecal flora at 24 hours. Which of the following additional tests would be most appropriate given the case history?
  - A. Heterophile antibody test
  - B. Rotavirus antigen assay of stool specimen
  - C. McCoy cell inoculation for cytomegalovirus (CMV)
  - D. Urine microscopic analysis for presence of CMV cellular inclusion bodies
27. Rhabdovirus is most noted for causing infections of the
  - A. Central nervous system
  - B. Gastrointestinal tract
  - C. Lower respiratory tract
  - D. Upper respiratory tract



28. Jaundice is a common clinical symptom of which of the following viral diseases?
- A. Hepatitis A
  - B. Infectious mononucleosis
  - C. Rabies
  - D. Varicella
29. An 18-year-old male presents to his family physician complaining of sore throat and fatigue. The patient is found to have a fever and swollen cervical lymph nodes. A complete blood count and differential reveal lymphocytosis and many reactive (atypical) lymphocytes. The physician should suspect an infection caused by
- A. Adenoviruses
  - B. Epstein-Barr virus
  - C. Parainfluenza virus
  - D. Varicella-zoster virus
30. The poliovirus, an RNA virus, is a(n)
- A. Adenovirus
  - B. Coxsackie virus
  - C. Enterovirus
  - D. Rhinovirus
31. The virus that causes hepatitis B is characterized as a
- A. Defective DNA virus requiring delta virus to complete its replication cycle
  - B. DNA virus utilizing reverse transcriptase
  - C. Nonenveloped DNA virus
  - D. Single-stranded RNA virus
32. Hepatitis C virus infections
- A. Are commonly diagnosed during the acute stage
  - B. Are uncommon in the U.S.
  - C. Are most often acquired by contact with blood
  - D. Seldom results in chronic infection
33. Characteristic cytopathic effect associated with respiratory syncytial virus is
- A. Giant multinucleated cells
  - B. Basophilic intranuclear inclusions
  - C. Eosinophilic cytoplasmic inclusions
  - D. Shrunken cells with multilobed nuclei
34. The virus associated with warts is
- A. Flavivirus
  - B. Morbillivirus
  - C. Mumps virus
  - D. Papillomavirus
35. RNA-dependent DNA polymerase is also called
- A. Gyrase
  - B. Neuraminidase
  - C. Reverse transcriptase
  - D. Transaminase
36. Coxsackie viruses are associated with
- A. Gastrointestinal disease
  - B. Hepatitis
  - C. Myocarditis
  - D. The common cold
37. The tubular cells of the human kidney shed which of the following viruses for prolonged periods?
- A. Adenovirus
  - B. Cytomegalovirus
  - C. Epstein-Barr virus
  - D. Rubella virus
38. The togavirus known to produce fetal defects is
- A. Influenza
  - B. Rotavirus
  - C. Rubella
  - D. Varicella

39. An 8-week-old infant was admitted to the hospital with symptoms of low birth weight, jaundice, and neurologic defects. Intranuclear inclusions were found in epithelial cells from the urine. The most likely diagnosis in this case would be infection by
- Cytomegalovirus
  - Epstein-Barr virus
  - Herpes simplex virus
  - Rubella virus
40. The most common cause of cervical cancer is
- Cytomegalovirus
  - Enterovirus
  - Molluscum contagiosum
  - Papillomavirus
41. Select the statement that is correct concerning the influenza A viruses.
- Humans are the only animal hosts for influenza A viruses.
  - Pandemics are characteristically produced by influenza A.
  - The incidence of infection peaks in the summer months.
  - They are DNA viruses.
42. An example of a virus associated with latent infections is
- Influenza
  - Rotavirus
  - Rubella
  - Varicella-zoster
43. The use of cell cultures has enabled virologists to isolate and identify many clinically important viruses. However, because some viruses cannot be grown in cell cultures, these agents are best diagnosed by serologic testing. Such an agent is
- Cytomegalovirus
  - Hepatitis C virus
  - Herpes simplex virus 2
  - Respiratory syncytial virus
44. Which of the following is associated with the rubella virus?
- It is a DNA virus.
  - It is a member of the same taxonomic family as measles virus.
  - It is known to produce defects in fetuses during the early stages of pregnancy.
  - It is transmitted by an arthropod vector.
45. Which of the following is *not* a step involved in virus replication?
- Attachment
  - Mitosis
  - Penetration
  - Release
46. Which of the following opportunistic diseases is *not* closely associated with acquired immune deficiency syndrome?
- Cryptococcosis
  - Cryptosporidiosis
  - Malaria
  - Mycobacteriosis
47. Although there have been no natural cases of this serious disease in about 30 years, which of the following is considered a potential bioterrorism disease
- Dengue
  - Ebola hemorrhagic fever
  - Shingles
  - Smallpox
48. Poliovirus is a member of the family
- Flaviviridae*
  - Paramyxoviridae*
  - Picornaviridae*
  - Reoviridae*

49. Which of the following has *not* been successfully used to detect viruses in clinical specimens?
- A. Cytopathic effect
  - B. Enzyme-linked immunosorbent assay
  - C. Growth on selective agar media
  - D. Immunofluorescence
50. Which of the following diseases is *not* associated with herpes simplex virus?
- A. Cold sores
  - B. Encephalitis
  - C. Genital herpes
  - D. Thrush



# answers

# & rationales

1.

**C.** Retroviruses are RNA viruses that replicate by means of DNA intermediates produced by the viral enzyme reverse transcriptase. The viruses associated with acquired immune deficiency syndrome are human immunodeficiency viruses (HIVs). These viruses belong to the family *Retroviridae*.

2.

**B.** Measles (rubeola) is a highly infectious childhood disease. Infection with this virus is followed by a prodromal syndrome characterized by cough, coryza, conjunctivitis, and fever. The most characteristic lesions, Koplik spots, are seen on the buccal mucosa. Koplik spots are diagnostic for measles infection and represent necrotic vesicles with a white center surrounded by erythema.

3.

**B.** Hepatitis B virus is an enveloped DNA virus transmitted by contact with blood or via sexual contact. Most hepatitis viruses have a long incubation period of several weeks to months. Hepatitis A and hepatitis E viruses are RNA viruses primarily spread via the fecal-oral route. Hepatitis C virus is an RNA virus transmitted by contact with blood.

4.

**A.** The last natural case of smallpox was in 1977, and the World Health Organization declared the world smallpox free in 1979. Elimination of the virus was due to a worldwide vaccination program. Because of the highly contagious nature of variola virus, the cause of smallpox, the ability of the virus to produce severe infections, and the termination of routine vaccinations, the virus is considered a potential bioterrorism agent.

5.

**B.** One of the major viral agents associated with cases of acute gastroenteritis in children is rotavirus. In particular, this agent is the cause of epidemic nonbacterial gastroenteritis in infants and young children that occurs most commonly during the winter months. Rotavirus belongs to the family of RNA viruses known as *Reoviridae*. Rotavirus has a fecal-oral route of transmission and has been documented as a nosocomial pathogen in pediatric areas of hospitals.

---

6.

**D.** During acquired immune deficiency syndrome (AIDS), as the immune system becomes weakened, the patient presents with chronic and recurrent infections and various neoplasms. Kaposi sarcoma, a relatively common cancer in patients with AIDS, has been linked to human herpes virus 8. Viral genome has been found in the cancerous growths in these patients.

---

7.

**A.** The human immunodeficiency viruses cause AIDS. The major target of the virus is the T helper cell, which would normally function to control disease. The virus initially binds to CD 4 found on the surface of T helper cells. Other coreceptors are also important for attachment.

---

8.

**C.** Commercially available cell cultures of human fibroblasts are optimal for the cultivation of cytomegalovirus (CMV). CMV will not replicate in other cell cultures such as HeLa or HEp-2. CMV can be identified with a high level of confidence solely on the basis of its characteristic cytopathology. Infected cells in the monolayer appear enlarged, rounded, and refractile.

---

9.

**A.** Adenoviruses are well known as respiratory pathogens and have been the cause of acute respiratory disease among military recruit populations. Also associated with adenoviral infection is the severe ocular disease keratoconjunctivitis, which typically occurs in epidemic form. Adenoviruses may remain in tissues, lymphoid structures, and adenoids and become reactivated.

---

10.

**D.** Cell cultures recommended for the isolation of herpes simplex virus (HSV) are human embryonic

fibroblasts. The usual period needed to detect HSV destruction of the cell monolayer is 1 to 2 days. The more common of the two recognized types of HSV cytopathic effect begins with a granulation of the cytoplasm followed by cell enlargement and a ballooned appearance. Monoclonal antibodies and immunofluorescence are commonly used to differentiate between HSV-1 and HSV-2.

---

11.

**B.** The Salk vaccine utilizes a formalin-inactivated poliovirus. The Sabin polio vaccine uses an attenuated virus; therefore, the virus is still able to infect cells and cause an asymptomatic infection. The Sabin vaccine provides a stronger immune response than the Salk vaccine.

---

12.

**A.** Members of the herpes virus group are responsible for a number of diseases, including cold sores. Hemorrhagic fevers are caused by a number of tropical viruses, such as Ebola and dengue. Polio is caused by a picornavirus, and rabies is caused by the rhabdovirus.

---

13.

**D.** Viruses are obligate intracellular parasites that cannot self-replicate. They cannot produce ATP, and their genome is surrounded by a protein capsid. Most viruses contain either DNA or RNA; however, some large DNA viruses do contain viral mRNA and microRNAs.

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14.

**C.** Zoster or shingles occurs predominantly in adults, whereas varicella occurs more commonly in children. The varicella-zoster virus, following the primary infection known as chicken pox, remains latent in the sensory ganglia. Reactivation of this virus, which occurs years later, is usually associated with a slightly immunocompromised state.

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15.

**D.** Rhinoviruses, members of the picornavirus group, are a common cause of the respiratory disease known as the common cold. Hand transmission, not aerosols, appears to be the primary means of transmission. In contrast to other picornaviruses, the optimum temperature for rhinoviruses is 33°C.

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16.

**B.** Influenza A virus undergoes recombination events that produce significant changes in the RNA genome of the virus. These changes lead to alteration of surface antigens. This process is referred to as antigenic shift. Antigenic drift is a slight change in a gene, usually a point mutation. Influenza A, B, and C viruses can undergo antigenic drift.

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17.

**D.** Rabies is a neurotropic virus that causes extensive destruction in the brain. Negri bodies are seen in the cytoplasm of large ganglion cells and are demonstrated by Seller's stain. Rabies in humans or lower animals can be diagnosed by demonstration of these characteristic inclusions. However, the more sensitive direct fluorescent antibody test is more commonly used.

---

18.

**D.** Molluscum contagiosum is an infectious disease with a worldwide distribution caused by a poxvirus. Nodules develop in the epidermis of the face, arms, back, and buttocks, which undergo necrosis. Examination of epithelioid cells from affected areas will show characteristic eosinophilic cytoplasmic inclusions (molluscum bodies).

---

19.

**A.** Prolonged storage of clinical specimens for viral isolation requires -80°C. Specimens can be stored at 4°C for approximately 48 hours without appreciable loss of viability. Specimens should not be stored at -20°C for any length of time.

---

20.

**D.** Arbovirus is short for arthropod-borne virus. These genetically diverse viruses share a common feature: They are transmitted by arthropods (e.g., mosquitoes and ticks). Arboviruses include West Nile virus and western equine encephalitis virus.

---

21.

**B.** The mumps virus infects the parotid glands. Infection results in swelling of the neck. Mumps is primarily a childhood infection, and swelling of the parotid glands is diagnostic.

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22.

**A.** Hepatitis A virus is typically transmitted by the fecal-oral pathway. Hepatitis B, C, and G viruses are generally transmitted by blood contact. Hepatitis E virus is also transmitted by the fecal-oral pathway.

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23.

**A.** Most enterovirus infections are probably asymptomatic. Despite the name, these viruses are rarely associated with infections of the gastrointestinal tract. When symptomatic, they are most noted for producing acute nonspecific febrile syndrome.

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**24.**

**A.** During the course of acute hepatitis B virus infection, hepatitis B surface antigen (HBsAg) is the first marker detected. The host will ultimately begin to produce antibody (anti-HBs) to the antigen. As the antibody titer increases, there is a corresponding decrease in the antigen. However, there is a time period when neither of these markers is detectable. During this time period the only serologic marker is antibody to the hepatitis B core antigen (anti-HBc). This period is called the core window.

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**25.**

**C.** Human herpes viruses (HHVs) 6 and 7 cause the childhood disease roseola, also called sixth disease. The disease is characterized by fever, rash, and sore throat. More cases are caused by HHV 6 than HHV 7.

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**26.**

**B.** Rotavirus is the cause of diarrheal disease in at least half of all infants and young children admitted to the hospital with dehydration requiring fluid replacement therapy. Because rotaviruses are difficult to propagate in cell culture, the method of choice for the detection of rotavirus infection is the direct examination of stool for the presence of viral antigen. Commonly used rotavirus antigen assay tests include latex agglutination and enzyme immunoassay.

---

**27.**

**A.** Rhabdovirus causes rabies, an infection of the central nervous system. The virus is transmitted in the saliva of an infected animal during a bite. At the bite site, the virus initially infects muscle tissue, but will move to the peripheral nerves. The virus then migrates along the peripheral nerves to the central nervous system.

---

**28.**

**A.** Hepatitis A is one of several infectious diseases characterized by liver damage and icterus (jaundice). The appearance of jaundice, in the icteric phase, is correlated by liver biopsy with extensive parenchymal destruction. Convalescence is usually accompanied by subsequent complete regeneration of the diseased organ.

---

**29.**

**B.** The Epstein-Barr virus, which is associated with Burkitt lymphoma and nasopharyngeal carcinoma, is the etiologic agent of infectious mononucleosis. Infectious mononucleosis is an acute disease most commonly affecting children and young adults. The virus is thought to be transmitted by intimate contact and has been called the “kissing disease.” The patient’s blood demonstrates a leukocytosis with a marked increase in T lymphocytes, and serologically the disease is characterized by a positive heterophile antibody and antibodies to various viral antigens.

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**30.**

**C.** Poliovirus, an enterovirus, is shed by both respiratory and fecal routes. Laboratory identification relies on isolation (especially from feces) and subsequent virus neutralization in tissue culture. Spread of the disease is associated with poor sanitary conditions and crowding.

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**31.**

**B.** The hepatitis B virus is an enveloped, partially double-stranded DNA virus. During viral replication, full-length RNA transcripts of the viral genome are inserted into maturing virus particles. The viral enzyme reverse transcriptase then transcribes these RNA transcripts to a full-length DNA strand but only partially completes synthesis of the complementary DNA strand—hence a partially double-stranded DNA genome.



32.

**C.** Hepatitis C virus infections, unlike hepatitis A or hepatitis B infections, do not commonly produce jaundice. There are tens of thousands of individuals in the United States chronically infected with hepatitis C; chronic infection appears to be the rule rather than the exception. Transmission of the virus at present occurs mainly through needle sharing. Cases also occur among healthcare workers who contact infected blood.

33.

**A.** Respiratory syncytial virus causes fusion of adjacent cells. This produces giant multinucleated cells called syncytia. Basophilic intranuclear and eosinophilic cytoplasmic inclusions are characteristic of cytomegalovirus infection.

34.

**D.** The etiologic agents for the numerous benign cutaneous and mucosal lesions known as warts are the human papillomaviruses (HPVs). The diagnosis of lesions caused by these agents is based on clinical appearance and histopathology, because there are no *in vitro* systems available for isolation. Some HPV types are strongly associated with squamous cell carcinoma of the cervix and anus.

35.

**C.** RNA-dependent DNA polymerase is also known as reverse transcriptase. The enzyme uses an RNA template to synthesize the complementary DNA strand. The retroviruses require this enzyme for replication.

36.

**C.** The coxsackieviruses are enteroviruses named after the town of Coxsackie, New York, where they were first isolated. The viruses are divided into groups A and B on the basis of viral and antigenic differences. The group B coxsackieviruses

are strongly associated with myocarditis that may cause sufficient damage to require heart transplantation. The group A coxsackieviruses are associated with various diseases, characterized by vesicular lesions, such as herpangina. Neither group of coxsackieviruses is associated with gastrointestinal disease.

37.

**B.** Cytomegalovirus infections may be asymptomatic for normal healthy hosts. Infections tend to be more severe in patients who are immunosuppressed or in neonates infected perinatally. Cytomegalovirus is readily isolated from urine because it is shed by the tubular cells of infected hosts.

38.

**C.** The rubella virus is an RNA virus and a member of the family *Togaviridae*. In adults and children, rubella infections are generally a mild contagious rash disease. When a pregnant woman becomes infected, the consequences become more serious. If the fetus is infected during the first trimester of pregnancy, a variety of congenital defects may result. Anatomic abnormalities produced by this agent include cataracts, deafness, and cardiac problems.

39.

**A.** Infants usually acquire cytomegalovirus infections before birth or at the time of childbirth. These infections may lead to death during the first month of life or may result in residual neurologic impairment. The virus can be isolated from several different body fluids, with urine being the most commonly examined.

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40.

**D.** Papillomaviruses are responsible for warts, including genital warts. Some serotypes of papillomavirus are associated with cervical cancer. A vaccine providing protection against these serotypes is available for women.

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41.

**B.** Influenza viruses are RNA viruses able to infect humans and other animals, such as birds and pigs. Influenza viruses are associated with epidemic and pandemic disease. There are two main types of influenza viruses (A and B), which differ antigenically and in epidemic periodicity. All recorded pandemics have been caused by influenza A viruses. The incidence of respiratory disease caused by these agents peaks during the winter months.

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42.

**D.** Herpes simplex viruses, cytomegalovirus, and varicella-zoster viruses (VZV) produce latent infections. The genomes of these viruses can remain dormant in host cells for decades. Shingles (zoster) represents reactivation of latent VZV.

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43.

**B.** Hepatitis C virus has never been grown in culture. All knowledge of the virus and diagnostic reagents has been attained through molecular techniques applied to the RNA genome. Hepatitis C virus infection can be diagnosed by detecting antibody to the virus or by amplifying viral RNA from plasma. Cytomegalovirus, herpes simplex virus, and respiratory syncytial virus are readily grown in culture.

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44.

**C.** The rubella virus causes an exanthematous disease resembling a milder form of measles in children. This single-stranded RNA virus, transmitted from person to person, is of medical importance to

females of childbearing years because of the teratogenic effects it has on the fetus. Congenital rubella, resulting from an intrauterine fetal infection, is most severe when contracted during the first trimester of gestation.

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45.

**B.** Lacking essential components for the synthesis of macromolecules, viruses are not able to reproduce by binary fission. Host cells are required to provide the synthesis of viral components. The replicative cycle has four stages: absorption, penetration (uncoating), eclipse (biosynthesis), and release (maturation). Viral replication in the host cell may result in cell death, chronic infection with no observable changes, or transformation of the infected cell into a cancerous cell.

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46.

**C.** The immunologic abnormalities demonstrated by patients with AIDS predispose them to a variety of opportunistic pathogens. The absence of a cellular and humoral immune response enables opportunistic organisms to cause extensive infection. Malaria is not an opportunistic infection.

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47.

**D.** Although smallpox has not caused a natural infection since 1977, it is regarded as a potential bioterrorism agent. Routine vaccination against smallpox is no longer in effect, so the majority of the world's population is again susceptible. The U.S. has stockpiles of vaccine available to vaccinate everyone in the country in case of an attack.

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48.

**C.** Poliovirus is a member of the family *Picornaviridae*. These are small RNA viruses lacking an envelope. Other members of the family include coxsackieviruses, echoviruses, enteroviruses, and rhinoviruses.

49. **C.** Because of their nature as obligate intracellular parasites, successful cultivation of viruses requires living cells. Cell cultures provide host cell systems, which are easily handled, stable for long periods, and not susceptible to host factors such as stress or physiologic changes. Viruses are not like bacteria; they will not grow on any cell-free medium.
50. **D.** Herpes simplex viruses (HSVs) are noted for causing a number of different diseases, notably cold sores (primarily HSV-1) and genital infections (primarily HSV-2). In neonates and immunocompromised individuals, they can produce encephalitis. They are also linked to severe eye infections. Thrush is an infection caused by the yeast *Candida*.

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